UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/534,487	03/24/2000	Lola M. Reid	114231.119	3384

27160 7590 07/13/2006

PATENT ADMINISTRATOR
KATTEN MUCHIN ROSENMAN LLP
1025 THOMAS JEFFERSON STREET, N.W.
EAST LOBBY: SUITE 700
WASHINGTON, DC 20007-5201

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/534,487	REID ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/19/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39 and 44-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39 and 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 09/115,920, now US Patent 6,146,899, which is a continuation of 08/751,546, now US Patent 5,789,246, which is a divisional of application 8/165,696, now US Patent 5,576,207, which is a continuation 7/741,128, now abandoned.

Applicants' amendment filed April 19, 2006 has been received and entered. Claims 1-38, 40-43 and 49 have been cancelled. Claims 39 and 44 have been amended. Claims 39, 44-48 are pending and currently under examination.

Claim Objections

Claim 39 objected to because it is dependent on canceled claim 43 is withdrawn.

Claim 49 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn.

Claim 49 has been canceled.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicants have summarized the basis of the invention (page 3), however have failed to address any of the specific point(s) raised in the previous rejection in arguments, relying instead on the claim amendments to overcome the rejection. The rejection below is formally a new

rejection because of the amendments to the claims, however re-emphasizes several issues raised in the previous rejection not addressed by the amendment to the claims, nor in arguments.

Claims 39, 44-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The literal support for "expanded" instead of enriched was noted in the previous rejection (see specification, top page 8), however it was noted that this portion of the specification did not support it in the context of delivery. This portion of the specification only provides support for cultured cells, and fails to support delivery "to a subject in need thereof". While other portions of the specification that provide support for subjects needing hepatocytes center on providing genetically altered hepatocytes to treat or prevent deficiencies in said subject (for example page 9 and 12), not precursors. Moreover, the delivery methods set forth in the dependent claim 48 are only supported on page 12, which is only in the context of delivering a genetically modified hepatocyte precursors. Importantly, it is noted that while the specification supports delivery to the spleen and portal venous system recited in the claim, it fails to provide recitation for delivery of the bile duct nor the peritoneum. Examiner noted that the specification contemplates that ""microcarrier beads, which are introduced (e.g., by injection) into the peritoneal space of recipient" (page 12), however fails to specifically contemplate cells in general by this route, or more specifically that the cells are into the peritoneum in general as instantly claimed.

Again, it is noted that the claims were not original claims, and were added after the first action on the merits of the application. It appears that the instant claims recite elements taken from throughout the specification however the elements were provided in various context, not in the methods of delivery as now claimed. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure"

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 29, 44-48 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Applicants have noted that such compositions are considered enabled as evidenced by the three issued patents, however enablement of a composition does not provide enablement for all its potential uses. In this case, in interpreting the breadth of the claims as noted above, the only "subject in need thereof" contemplated by the instant specification are subjects which should be administered genetically altered hepatocyte precursor, presumably with a genetic modification that would remedy a great breadth of any potential problem associated with any particular subjects liver. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims; the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01(a)). The specification is not enabling for the claimed invention because the specification does not provide sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the invention as claimed invention without undue experimentation.

The instant claims encompass a method for treating any liver dysfunction (e.g., as a result of primary liver diseases such as hepatitis infection, toxin-induced liver failure, alcoholic liver disease, hepatocarcinoma, cirrhosis, fibrosis) in any patient in need thereof through the administration of hepatoblasts derived from any source (autologous, allogeneic and xenogenic

livers including embryonic, neonatal and adult livers). The state and the unpredictability of the art at the effective filing date of the present application (January 19, 1993), the art on liver stem cells or liver progenitor cells or hepatoblasts was still in its infancy as recognized by Applicants (see specification), and it is still controversial even several years after the effective filing date of the present application as evidenced by the review article of Kay *et al.* (Molecular Medicine Today 3:108-115, 1997). Kay *et al.* asked "Can true human liver stem-cells be identified, isolated and manipulated for therapeutic purposes?" (page 114), and stated "There is no evidence to suggest that stem cells are the source of replicating cells in the regenerating liver after partial hepatectomy. Instead, studies performed over more than three decades show that hepatocytes replicate" (column 2, last paragraph, page 109). Furthermore, even in year 2000, Shafritz stated 'since liver transplantation is the only available current therapy for end-stage liver failure and there is an ever-increasing shortage of donor livers, finding alternative methods for liver replacement is of utmost importance" (Shafritz, D.A., (American Journal of Hepatology 32:1399-1400, 2000). Additionally, Dabeva *et al.* (Pathology 156:39-47, 2000) demonstrated for the first time, many years after the effective filing date of the present application, that upon infusion isolated early (E14) fetal liver epithelial cells (FLEC) into the liver through the portal vein, these cells can proliferate, differentiate in the liver of syngeneic adult rats into mature hepatocytes and bile duct epithelial cells onlv under cedain exnerimental conditions such as the liver being subjected to partial hepatectomy or treated with proliferative stimuli (page 2029, col. 1, middle paragraph). Furthermore, it is uncertain whether the FLEC population taught by Dabeva *et al.* even has the same physiological or biological activity as the hepatoblast cell populations disclosed by the instant invention. Dabeva *et al.* further noted that although several studies have

reported successful engraftment and differentiation of early fetal liver tissue or cell suspensions after transplantation into ectopic sites, the engrafted liver tissue masses at ectopic sites do not expand very 2 much, and that it is unlikely that such limited liver transplantation will have broad therapeutic application (see col. 2, page 2029, last sentence continues to the top of page 2030).

The specification only provides conditions and methods for isolating the precursor cells in the context of a composition of cells (see for example US Paten 6,146,889) and does not provide any guidance to isolate a population of hepatocyte precursor cells as a starting material as required by the instantly claimed methods or as present in the drug delivery system. Two main points of enablement are at issue; first, the ability of the disclosed composition of precursor cells to serve as hepatocyte precursor cells for treatment when placed into a subject, and second the lack of necessary guidance and skill in the art to provide treatment of a specific liver dysfunction by genetically engineering a hepatocyte precursor cell.

The specification teaches the isolation of a composition of cells which comprises hepatocyte precursor cells from the liver (entire specification, summarized on page 2; lines 1-5), and that culturing the precursor cells with liver stromal cells and an extracellular matrix one can effectively increase the number of said precursor cells (summarized on page 7; lines 13-18). The specification provides evidence that hepatocyte precursor cells exist in a composition of cells isolated from total liver, however the specification fails to provide the necessary guidance or details on how one would isolate the materials, i.e. hepatocyte precursor cells, to practice the instantly claimed method or make the drug delivery system. More importantly, the specification does not provide any substantive teaching nor examples demonstrating that hepatocyte precursor cells isolated in this manner will maintain a precursor like state or will differentiate into mature

hepatocytes *in vitro* or *in vivo* if engrafted back into a subject. The specification presents only a prophetic description for the potential use of the hepatocyte precursor cells in obtaining a genetically engineered hepatocyte precursor but does not demonstrate that one can isolate, culture or place these cells back into an *in vivo* context in a subject by any means as required by the instant claims.

In addition, it is noted that the term hepatocyte precursor recited in the claims is not specifically defined in the specification, however is indicated to be used to describe a cell population that has been culture under conditions which result in expansion of the immature cells (page 1, lines 16-17). This term as broadly described and supported by the instant specification encompasses immature cells from any source obtained by any means. This interpretation of the breadth of the claim is more specifically supported by the specification stating that the precursor cells can be obtained sources other than the liver, sources, such as, but not limited to, the pancreas, gut, lung, and bone marrow (page 1, lines 22-24). The specification provides no specific epitopes for the contemplated precursor cells, potentially supporting only the absence of specific genes which are expressed in more differentiated cells. As noted in Applicants' arguments, Examiner acknowledges that the capability of a hepatocyte precursor cells to differentiate into a hepatocyte is a necessary and defining characteristic of a hepatocyte precursor cell (Applicants' after final amendment top of page 11; Examiners action paper number 7, page 13), however the specific basis of the rejection is that the specification fails to provide the necessary guidance or details of the identifying features of these cells which are indicative or predict this characteristic. The specification provides general guidance for mincing and dissociating cells of a tissue, and reduces to practice the culturing of a composition of cells

isolated from liver. At the time of filing and today the artisan believed that the liver contained stem cells, therefore it would not be contested that the facile methodology reduced to practice resulted in a composition of cells which comprised hepatocyte precursor cells, however while stem cells may exist in other tissues there is no evidence of record that hepatocyte precursor cell exists in other tissues. Further, while other culturing conditions are generally contemplated, the specification fails to provide the means to these specific conditions. Moreover, without any specific or defining feature of a hepatic precursor cell maintained in the disclosed composition of cultured cells, the skilled artisan would not even be able to optimize conditions if such a precursor cell existed in tissues other than the liver. Examiner acknowledges the subject matter that has been set forth in US patents to which the instant application claims priority, however the subject matter determined to be enabled and patentable is not equal in scope with that instantly claimed. Importantly in this case, the instant claims do not use or require the composition of cells claimed in US patent 5,789,246. Further, it is noted that patentability of a product only requires one enabled use and does not by itself enable all potential uses of said product, and therefore would not provide a presumptive rebuttal of a *prima facie* case of lack of enablement for any method using said product. In this case the claims to the allowed product are not the same as the product used in the instantly claimed methods, nor does the existence of such a cell in a composition provide for any prophetic use of said cell.

Applicants have previously provided several post filing references for support of use of stem cells in therapeutic methods, in particular for the delivery of a transgene. The ability to make a genetically altered cell by transforming a cell with a gene of interest in culture is not at issue. Examiner acknowledges that specific methodology for models of *ex vivo* gene therapy are

currently being developed in the art. With respect to the references provided by Applicants, the only reference relevant to the instantly claimed method is that of Dabeva *et al.* because the remaining references deal with hematopoietic stem cells not hepatocyte precursor cells. Hematopoietic stem cells are present in the circulation or bone marrow and can only be used in particular therapies associated with lineages of these cell types. None of the specific methodology or genes of interest for this technology would be applicable to the instantly claimed methods. With respect to the teachings of Debeva *et al.* initially it is noted that the FLEC used by Debeva *et al.* are not the same as used in the instantly claimed methods, nor are they obtained by the methods disclosed in the instant specification therefore does not by itself provide evidence that the cells disclosed in the instant specification and used in the instantly claimed method would differentiate into hepatocytes when placed into the liver of a subject. Even if one to concede that the hepatocyte precursor cells present in the composition of cells enabled by the instant application would differentiate *in vivo*, Debeva *et al.* teach that the method needed to successfully engraft cells into the liver require partial hepatectomy which is not taught in the instant specification. The specification recites the potential usefulness of genetically engineered hepatocyte precursor cells for treatment of liver dysfunction, and provides a curt description of methodology for inserting a gene of interest and administering said cell for treatment, wherein treatment is affected by expression of a missing or mutated endogenous gene, expression of antisense polynucleotides to suppress expression of an undesired gene (pages 12-14; starting at line 4). With respect to instant application, there is no specific guidance nor examples on how one would treat any liver dysfunction. For example, the specification provides a general description of how one could treat hypercholesteremia by expressing the LDL gene in said cells,

however there is no specific guidance on the type of promoter to use, the level of LDL expression one would need to treat a subject or if these cells would proliferate in a subject, how many cells to transplant. Another example describes the treatment of hepatitis infection by expression of anti-sense polynucleotides, however there is no guidance to what oligonucleotides would generate any treatment, what levels of expression one need to inhibit any function of any aspect of viral pathology, or how expression of a polynucleotide in a transplanted cell would affect any form of treatment in other surrounding cells. There is no guidance in the specification nor the art of record on how one would target and insert a gene of interest into said cells to create a genetically modified cell. The present specification has not provided any guidance to serve as a nexus between the art recognized obstacles of gene therapy protocols and treatment of any liver dysfunction.

Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Applicants have described a method to isolate a composition of cells comprising hepatocyte precursor cells from the liver, however essentially all of the work required to genetically engineer the cells with the appropriate gene for a particular liver dysfunction, use of the cells for treatment *in vivo*, and the proper route of administration to affect treatment has been left for others.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Newly Amended claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 39 has been amended to be dependent on claim 44 which is a method of "providing mature hepatocytes", not a method "of treatment" as indicated in claim 39. There is insufficient antecedent basis for "The method of treatment" recited in the claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 44-48 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35-41 of copending Application No. 10/127,697 (US 2003/0086910 A1).

Applicants request that the rejection be stayed until a notice of allowable claims is provided. Applicants' request is noted, however a rejection can not be held in abeyance.

It is noted that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because each comprise a method of administering progenitor cells which differentiate *in vivo* into hepatocytes. Each set forth dependent claims of embodiments from where the cells are isolated and how the cells are administered.

Applicant was advised that should claim 45 were to be found allowable, claim 39 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

Applicants have not addressed this issue in their response.

Again, it is noted that when two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 39 was amended to be dependent on the only independent claim 44, and it is now a duplicate of claim 45. While claim 39 recites "treatment", the steps of affecting this encompassed by claim 44 simply require delivery which is also encompassed by claim 45.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at 571 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach